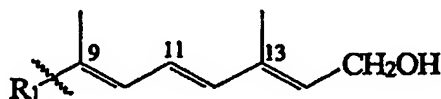


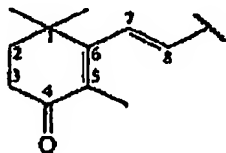
WHAT IS CLAIMED IS:

1. A method of treating a subject suffering from a disorder characterized by abnormal cell-proliferation and/or cell-differentiation, comprising administering to the subject in need of such treatment a pharmaceutically effective dose of a growth factor receptor inhibitor and a retinoid wherein:

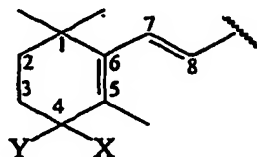
the retinoid is selected from the group of retinoid D with an alcohol CH<sub>2</sub>OH terminal side chain, an ester of retinoid D having an ester bond, an ether of retinoid D having an ether bond, retinoid D where the alcohol CH<sub>2</sub>OH terminal side chain is replaced with an aldehyde CHO terminal side chain, retinoid D with a carboxylic acid at the terminal side chain wherein each of the ester bond and the ether bond is formed with the oxygen at the terminal side chain of Retinoid D and wherein retinoid D with the alcohol CH<sub>2</sub>OH terminal side chain has the structure:



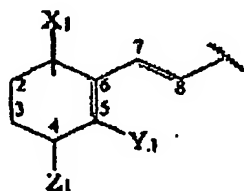
wherein the configuration at the 7-, 9-, 11- and 13-position double bonds is independently Z or E and wherein R<sub>1</sub> is selected from the group of



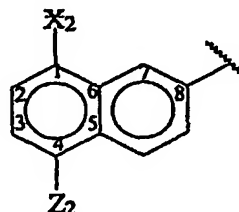
wherein the keto group at the 4-position is free or protected, or is replaced by a thioketone group which is free or protected or is replaced by C<sub>1-6</sub>-alkylidene group;



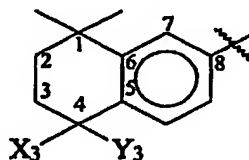
wherein X is selected from the group of hydrogen and C<sub>1-6</sub>-alkyl and Y is selected from the group of C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino and wherein the absolute configuration at the 4-position is independently R or S;



wherein X<sub>1</sub>, Y<sub>1</sub> are independently selected from the group of hydrogen, C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino and Z<sub>1</sub> is selected from the group of C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino;

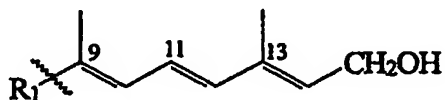


wherein X<sub>2</sub> is selected from the group of hydrogen, C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino and Z<sub>2</sub> is selected from the group of C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino;

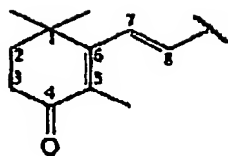


wherein  $X_3$  and  $Y_3$  are independently selected from the group of hydrogens,  $C_{1-6}$ -alkyl, hydroxyl,  $C_{1-6}$ -alkoxyl,  $C_{1-6}$ -acyloxyl, halide, azide, sulfhydryl, amine and  $C_{1-6}$ -alkyl substituted amino so long as  $X_3$  and  $Y_3$  are not both hydrogens.

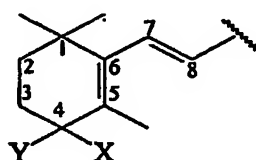
2. The method of claim 1, wherein the retinoid retinoid D with the alcohol CH<sub>2</sub>OH terminal side chain has the structure:



wherein the configuration at the 7-, 9-, 11- and 13-position double bonds is independently Z or E and wherein R<sub>1</sub> is selected from the group of:



wherein the keto group at the 4-position is free or protected; and



wherein X is selected from the group of hydrogen and C<sub>1-6</sub>-alkyl and Y is selected from the group of hydroxy and C<sub>1-6</sub>-alkyoxyl and wherein the absolute configuration at the 4-position is independently R or S.

3. The method of claim 1, wherein the retinoid is retinoid D with an alcohol CH<sub>2</sub>OH terminal side chain.

4. The method of claim 1, wherein the retinoid is selected from the group of 4-oxo-retinol, 4-oxo-retinoic acid, 4-oxo-retinal, and 4-oxo-retinyl ester.

5. The method of claim 1, wherein the retinoid is all-trans 4-oxo-retinol or an isomer thereof.

6. The method of claim 1, wherein the retinoid is 4-hydroxy-retinol.

7. The method of claim 1, wherein the retinoid is 4-methoxy-retinol.
8. The method of claim 1, wherein said growth factor receptor is EGF receptor.
9. The method of claim 8, wherein said EGF receptor inhibitor is an EGF receptor antibody.
10. The method of claim 9, wherein said antibody is C-225.
11. The method of claim 8, wherein said EGF receptor inhibitor is an inhibitor of tyrosine kinase activity mediated by EGF receptors.
12. The method of claim 11, wherein said EGF receptor inhibitor is IRESSA®.
13. The method of claim 1, wherein said growth factor receptor is TGF-alpha.
14. The method of claim 1 further comprising administering to the subject a vitamin D analog.

15. The method of claim 14, wherein the vitamin D analog is selected from the group of cholecalciferol, calcifediol, calcitriol, calcipotriol, ergocalciferol, dihydrotachysterol, 1,25-dihydroxyergocalciferol, and 25-hydroxydihydrotachysterol.

16. The method of claim 15, wherein the vitamin D analog is calcitriol.

17. The method of claim 15, wherein the vitamin D analog is calcipotriol.

18. The method of claim 1 further comprising administering to said subject at least one chemotherapy agent.

19. The method of claim 1 further comprising treating said subject with irradiation.

20. The method of claim 1, wherein said disorder is cancer.

21. The method of claim 20, wherein said cancer is selected from the group of: melanoma, superficial squamous cell cancer of the skin, keratoacanthoma, head and neck cancers, thyroid cancer, lung both Non Small and Small cell lung cancer, thymoma, teratocarcinoma, hepatoma, gastric, brain, esophageal, pancreatic, cholangiocarcinoma, ampullary carcinoma, carcinoid, small bowel cancer, colon, appendiceal, rectal, anal, ovarian, breast, uterine or

endometrial, fallopian tube, vaginal, cervical, penile, testicular, prostate, renal cell or kidney, lymphoma, acute leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, osteosarcoma, sarcoma, glioma, astrocytoma, multiple myeloma, glioblastoma multiforme and ependymoma.

22. A method of treating a subject suffering from a disorder characterized by abnormal cell-proliferation and/or cell-differentiation, comprising administering to the subject in need of such treatment a pharmaceutically effective dose of a growth factor receptor inhibitor and a retinoid that binds and/or transactivates a Retinoic Acid Receptor or RXR.

23. The method of claim 22, wherein the retinoid is selected from the group of retinoic acid, retinamide, bexarotene and tazarotene.

24. The method of claim 22, wherein the Retinoid Acid receptor (RAR) is selected from the group of:  $RAR\alpha$ ,  $RAR\beta$  and  $RAR\gamma$ .

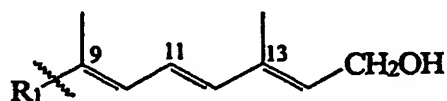
25. The method of claim 22, wherein the RXR is selected from the group of:  $RXR\alpha$ ,  $RXR\beta$  and  $RXR\gamma$ .

26. The method of claim 23, wherein the retinoic acid is selected from the group of isomers of: all-trans-retinoic acid, 9-cis-retinoic acid and 13-cis-retinoic acid.

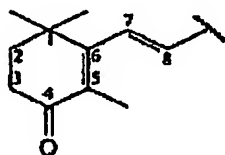
27. The method of claim 23, wherein the retinoid is bexarotene, the disorder is non small cell lung cancer and the growth factor receptor inhibitor is IRESSA®.

28. A method of treating a subject suffering from cancer, comprising administering to the subject in need of such treatment a pharmaceutically effective dose of a retinoid wherein:

the retinoid is selected from the group of retinoid D with an alcohol CH<sub>2</sub>OH terminal side chain, an ester of retinoid D having an ester bond, an ether of retinoid D having an ether bond, retinoid D where the alcohol CH<sub>2</sub>OH terminal side chain is replaced with an aldehyde CHO terminal side chain, retinoid D with a carboxylic acid at the terminal side chain wherein each of the ester bond and the ether bond is formed with the oxygen at the terminal side chain of Retinoid D and wherein retinoid D with the alcohol CH<sub>2</sub>OH terminal side chain has the structure:

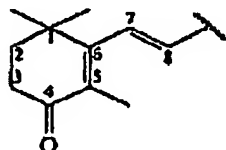


wherein the configuration at the 7-, 9-, 11- and 13-position double bonds is independently Z or E and wherein R<sub>1</sub> is selected from the group of

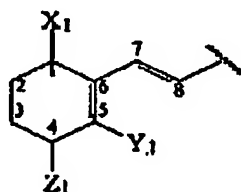




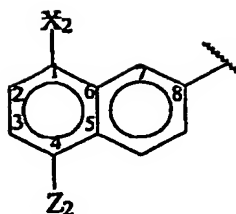
wherein the keto group at the 4-position is free or protected, or is replaced by a thioketone group which is free or protected or is replaced by C<sub>1-6</sub>-alkylidene group;



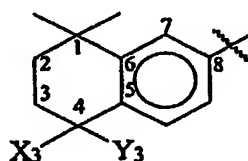
wherein X is selected from the group of hydrogen and C<sub>1-6</sub>-alkyl and Y is selected from the group of C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino and wherein the absolute configuration at the 4-position is independently R or S;



wherein X<sub>1</sub>, Y<sub>1</sub> are independently selected from the group of hydrogen, C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino and Z<sub>1</sub> is selected from the group of C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino;



wherein  $X_2$  is selected from the group of hydrogen,  $C_{1-6}$ -alkyl, hydroxyl,  $C_{1-6}$ -alkoxyl,  $C_{1-6}$ -acyloxyl, halide, azide, sulfhydryl, amine and  $C_{1-6}$ -alkyl substituted amino and  $Z_2$  is selected from the group of  $C_{1-6}$ -alkyl, hydroxyl,  $C_{1-6}$ -alkoxyl,  $C_{1-6}$ -acyloxyl, halide, azide, sulfhydryl, amine and  $C_{1-6}$ -alkyl substituted amino;



wherein  $X_3$  and  $Y_3$  are independently selected from the group of hydrogens,  $C_{1-6}$ -alkyl, hydroxyl,  $C_{1-6}$ -alkoxyl,  $C_{1-6}$ -acyloxyl, halide, azide, sulfhydryl, amine and  $C_{1-6}$ -alkyl substituted amino so long as  $X_3$  and  $Y_3$  are not both hydrogens; and

wherein said cancer is selected from the group: melanoma, superficial squamous cell cancer of the skin, keratoacanthoma, head and neck cancers, thyroid cancer, lung both Non Small and Small cell lung cancer, thymoma, teratocarcinoma, hepatoma, gastric, brain, esophageal, pancreatic, cholangiocarcinoma, ampullary carcinoma, carcinoid, small bowel cancer, colon, appendiceal, rectal, anal, ovarian, uterine or endometrial, fallopian tube, vaginal, cervical, penile, testicular, prostate, renal cell or kidney, lymphoma, acute lymphoblastic leukemia, acute leukemia,

chronic lymphocytic leukemia, chronic myelogenous leukemia, osteosarcoma, sarcoma, glioma, astrocytoma, multiple myeloma, glioblastoma multiforme and ependymoma.

29. The method of claim 28 further comprising administering to the subject a vitamin D analog.

30. The method of claim 29, wherein the vitamin D analog is selected from the group of cholecalciferol, calcifediol, calcitriol, calcipotriol, ergocalciferol, dihydrotachysterol, 1,25-dihydroxyergocalciferol, and 25-hydroxydihydrotachysterol.

31. The method of claim 30, wherein the vitamin D analog is calcitriol.

32. The method of claim 30, wherein the vitamin D analog is calcipotriol.

33. The method of claim 28 further comprising administering to said subject at least one chemotherapy agent.

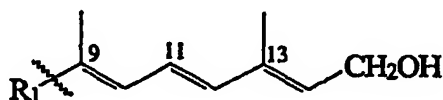
34. The method of claim 28 further comprising treating said subject with irradiation.

35. The method of claim 28, wherein said cancer is acute lymphoblastic leukemia.

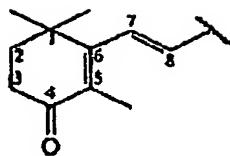
36. The method of claim 28, wherein said cancer is Non Small cell lung cancer.

37. A pharmaceutical composition comprising a pharmaceutically effective dose of a growth factor receptor inhibitor and retinoid wherein:

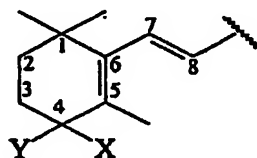
the retinoid is selected from the group of retinoid D with an alcohol  $\text{CH}_2\text{OH}$  terminal side chain, an ester of retinoid D having an ester bond, an ether of retinoid D having an ether bond, retinoid D where the alcohol  $\text{CH}_2\text{OH}$  terminal side chain is replaced with an aldehyde  $\text{CHO}$  terminal side chain, retinoid D with a carboxylic acid at the terminal side chain wherein each of the ester bond and the ether bond is formed with the oxygen at the terminal side chain of Retinoid D and wherein retinoid D with the alcohol  $\text{CH}_2\text{OH}$  terminal side chain has the structure:



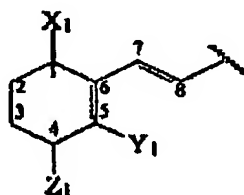
wherein the configuration at the 7-, 9-, 11- and 13-position double bonds is independently Z or E and wherein  $\text{R}_1$  is selected from the group of



wherein the keto group at the 4-position is free or protected, or is replaced by a thioketone group which is free or protected or is replaced by C<sub>1-6</sub>-alkylidene group;

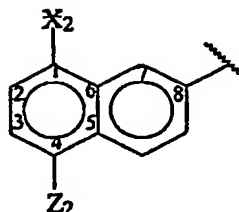


wherein X is selected from the group of hydrogen and C<sub>1-6</sub>-alkyl and Y is selected from the group of C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino and wherein the absolute configuration at the 4-position is independently R or S;

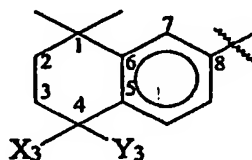


wherein X<sub>1</sub>, Y<sub>1</sub> are independently selected from the group of hydrogen, C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino and Z<sub>1</sub> is selected from the group of C<sub>1-6</sub>-alkyl,

hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino;



wherein X<sub>2</sub> is selected from the group of hydrogen, C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino and Z<sub>2</sub> is selected from the group of C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino;



wherein X<sub>3</sub> and Y<sub>3</sub> are independently selected from the group of hydrogens, C<sub>1-6</sub>-alkyl, hydroxyl, C<sub>1-6</sub>-alkoxyl, C<sub>1-6</sub>-acyloxyl, halide, azide, sulfhydryl, amine and C<sub>1-6</sub>-alkyl substituted amino so long as X<sub>3</sub> and Y<sub>3</sub> are not both hydrogens.

38. The composition of claim 37, wherein the retinoid is selected from the group of 4-oxo-retinol, 4-oxo-retinoic acid, 4-oxo-retinal, and 4-oxo-retinyl ester.

39. The composition of claim 37, wherein the retinoid is all-trans 4-oxo-retinol or an isomer thereof.

40. The composition of claim 37, wherein the retinoid is 4-hydroxy-retinol.

41. The composition of claim 37, wherein the retinoid is 4-methoxy-retinol.

42. The composition of claim 37, wherein said growth factor receptor is EGF receptor.

43. The composition of claim 42, wherein said EGF receptor inhibitor is an EGF receptor antibody.

44. The composition of claim 43, wherein said antibody is C-225.

45. The composition of claim 42, wherein said EGF receptor inhibitor is an inhibitor of tyrosine kinase activity mediated by EGF receptors.

46. The composition of claim 42, wherein said EGF receptor inhibitor is IRESSA®

47. The composition of claim 37, wherein said growth factor receptor is TGF-alpha.